

research

Outcome of severe infections in afebrile neutropenic cancer patients

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Radiol Oncol 2016; 50(4): 442-448.

Received: 28 October 2015

Accepted: 5 November 2015

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Disclosure: The authors declare no conflict of interest.

Results of this analysis were in part presented at the MASCC/ISOO International Symposium on Supportive Care in Cancer in New York City in 2012 (oral presentation of the abstract #734).

Background. In some neutropenic cancer patients fever may be absent despite microbiologically and/or clinically confirmed infection. We hypothesized that afebrile neutropenic cancer patients with severe infections have worse outcome as compared to cancer patients with febrile neutropenia.

Patients and methods. We retrospectively analyzed all adult cancer patients with chemotherapy-induced neutropenia and severe infection, who were admitted to the Intensive Care Unit at our cancer center between 2000 and 2011. The outcome of interest was 30-day in-hospital mortality rate. Association between the febrile status and in-hospital mortality rate was evaluated by the Fisher's exact test.

Results. We identified 69 episodes of severe neutropenic infections in 65 cancer patients. Among these, 9 (13%) episodes were afebrile. Patients with afebrile neutropenic infection presented with hypotension, severe fatigue with inappetence, shaking chills, altered mental state or cough and all of them eventually deteriorated to severe sepsis or septic shock. Overall 30-day in-hospital mortality rate was 55.1%. Patients with afebrile neutropenic infection had a trend for a higher 30-day in-hospital mortality rate as compared to patients with febrile neutropenic infection (78% vs. 52%, $p = 0.17$).

Conclusions. Afebrile cancer patients with chemotherapy-induced neutropenia and severe infections might have worse outcome as compared to cancer patients with febrile neutropenia. Patients should be informed that severe neutropenic infection without fever can occasionally occur during cancer treatment with chemotherapy.

Key words: afebrile infection; fever; neutropenia; hypothermia; cancer

Introduction

Infections are important cause of morbidity and mortality in cancer patients.¹ Neutropenia is a major risk factor for the development of infection in cancer patients undergoing treatment with chemotherapy.^{2,3} Fever remains the most prevalent and evident sign of infection in neutropenic cancer patients and early initiation of broad-spectrum antibiotic therapy significantly reduces mortality in these patients.⁴⁻⁷

Fever is a phylogenetically ancient host defense response to variety of infectious and non-infectious triggers. It is a result of upregulation of the hypothalamic thermostatic set point due to the complex interplay between endogenous and exogenous pyrogens, enzymatic and neuronal pathways and endogenous antipyretic neuropeptides and hormones.⁸⁻¹¹ Pyrogenic cytokines concurrently trigger production of acute phase reactants and stimulate activation of various metabolic, endocrinologic and immunologic systems.¹² Data from clinical

observations and observational studies show that fever may have a beneficial effect on morbidity and mortality caused by the non-life-threatening infections.^{8,11,12} However, in some neutropenic cancer patients fever may be absent despite microbiologically and/or clinically confirmed infection.⁵ According to the Infectious Disease Society of America (IDSA) and some other guidelines afebrile neutropenic patients with new signs or symptoms of infection are considered to be at high-risk for complications and therefore prompt use of empirical antimicrobial agents is recommended.¹³⁻¹⁵ Nevertheless, the level of evidence for this recommendation is weak (B-III) and is based on the extensive clinical experience of the Panel members.¹³

Afebrile infections are not unique to neutropenic cancer patients. Even more, published data shows that non-neutropenic patients with afebrile severe infections, especially those with hypothermia, have higher mortality rates compared to febrile non-neutropenic patients.^{8,16,17}

We conducted a retrospective study to evaluate the incidence and characteristics of severe infections in afebrile neutropenic cancer patients undergoing treatment with chemotherapy at our cancer center. Furthermore, we hypothesized that afebrile neutropenic cancer patients with severe infections have worse outcome as compared to cancer patients with febrile neutropenia.

Patients and methods

Study population and data collection

We performed an electronic database search to identify all adult cancer patients, who were transferred from the Department of Medical Oncology to the Intensive Care Unit (ICU) at the Institute of Oncology Ljubljana due to the severe neutropenic infection between January 2000 and December 2011. All eligible patients for this study were required to have a severe infection due to a chemotherapy-induced neutropenia. Multiple episodes of neutropenic infections in one patient were considered as separate events. All information on relevant patients' characteristics, cancer treatment and episodes of infections were retrieved retrospectively from patients' charts. All data were extracted by a single author.

Febrile neutropenic infections were defined as at least one axillary body temperature measurement of $\geq 38^{\circ}\text{C}$ in the presence of neutropenia (absolute neutrophil count $< 1 \times 10^9/\text{l}$ at the time of diagnosis

of infection with further decline to $< 0.5 \times 10^9/\text{l}$ during the following days). Afebrile neutropenic infections were defined as a maximum axillary body temperature $< 38^{\circ}\text{C}$ within 72 hours of diagnosis of neutropenic infection, which had to be microbiologically and/or clinically documented. Severe neutropenia was defined as an absolute neutrophil count $\leq 0.1 \times 10^9/\text{l}$.

Infection was considered microbiologically documented when a positive culture was yielded from the site of infection, and clinically documented when there were clinical and/or radiological signs of infection without microbiological confirmation. Characteristics of organisms isolated from blood cultures were recorded. At least two positive blood culture sets were required when *coagulase-negative staphylococci* or other potential skin contaminants (e.g. *Corynebacterium* spp., *Propionibacterium* spp., *Bacillus* spp.) were isolated. Polymicrobial bacteremia was defined as more than one organism isolated from blood culture specimens obtained within 24 hours of the first positive blood culture specimen in a single patient.¹⁸

We calculated the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index score for each patient as described by Klastersky *et al.*¹⁹ Comorbidities were evaluated using the adult comorbidity evaluation-27 index (ACE-27) and Charlson comorbidity index (CCI).^{20,21} Severe sepsis and septic shock were defined according to the established 2001 International Sepsis Definitions Conference criteria.²²

Our retrospective study was approved by the Institutional Review Board and Ethics Committee (#ERID-KESOPKR/74).

Statistical analysis

We used descriptive statistics to describe relevant patients' characteristics. The outcome of interest was 30-day in-hospital mortality rate, as proposed by Feld *et al.*²³ Association between the outcome and different prognostic factors and comparison of different characteristics between febrile and afebrile patients were evaluated using Chi-square or Fisher's exact test as appropriate. To compare mean time from the diagnosis of neutropenic infection to the ICU admission between afebrile and febrile patients we used independent-samples t-test. Due to the small number of events a multivariate analysis was not feasible. All significance tests were two-sided using an alpha level of 0.05. No correction was applied for multiple statistical testing.

TABLE 1. Baseline patients' characteristics, cancer type and treatment

Characteristics		N (%) (n = 69)
Median age (range)	Elderly (> 65 years)	58 years (31–86) 28 (40.6%)
Sex	Male	42 (60.9%)
	Female	27 (39.1%)
Cancer type	Lymphoma	52 (75.4%)
	Solid tumors	17 (24.6%)
Chemotherapy treatment intent	Neo/adjuvant solid or 1 st -line lymphoma	35 (50.7%)
	1 st -line solid or 1 st -relaps lymphoma	13 (18.8%)
	2 nd -line solid or 2 nd -relaps lymphoma	12 (17.4%)
	≥ 3 rd -line solid or ≥ 3 rd -relaps lymphoma	9 (13.1%)
CCI	Low (0)	28 (40.6%)
	Medium (1–2)	30 (43.5%)
	High (3–4)	8 (11.6%)
	Very high (≥ 5)	3 (4.3%)
ACE-27	None (G0)	17 (24.6%)
	Mild (G1)	16 (23.2%)
	Moderate (G2)	13 (18.9%)
	Severe (G3)	23 (33.3%)
WHO performance status	0–2	54 (78.3%)
	3–4	15 (21.7%)
Bone marrow infiltration	Yes	22 (31.9%)
	No	29 (42.0%)
	Unknown	18 (26.1%)
Previous neutropenic infection	Yes	24 (34.8%)
	No	45 (65.2%)
Site of infection ^a	Bloodstream	25 (36.2%)
	Lower respiratory tract ^b	25 (36.2%)
	Gastrointestinal tract ^c	13 (18.8%)
	Upper respiratory tract	2 (2.9%)
	Urinary tract	1 (1.5%)
	Skin and soft tissue	1 (1.5%)
	Unexplained fever ^d	2 (2.9%)
Time period of ICU admission (year)	2000–2003	8 (13.6%)
	2004–2011	51 (86.4%)

ACE-27 = adult comorbidity evaluation-27 index; CCI = Charlson comorbidity index; ICU = Intensive Care Unit; WHO = World Health Organization

^a Includes 53 episodes of microbiologically documented infection (MDI) and 16 episodes of clinically documented infection (CDI)

^b Pneumonias with 13 cases of MDI and 12 cases of CDI with radiological signs only

^c Includes cases of cholecystitis, peritonitis, neutropenic enterocolitis

^d CDI with fever and signs of septic shock

Results

Study population

We identified 69 episodes of neutropenic infections in 65 cancer patients treated with chemotherapy, who required admission to the ICU during the 11-year period. Four patients had two separate episodes of febrile neutropenic infection. Baseline patients' characteristics, cancer type and treatment are summarized in Table 1.

Patients received a median of one cycle (range 1–9 cycles) of treatment with chemotherapy prior to the episode of neutropenic infection. Median overall length of hospitalization and hospitaliza-

tion in the ICU were 14 days (range 1–52 days) and 5 days (range 1–34 days), respectively.

A median MASCC score was 14 (range 0–21). Only two episodes were considered low-risk according to the MASCC score. In the remaining 67 high-risk episodes, 35 had the MASCC score < 15. Thirty patients (43.5%) had severe neutropenia at the onset of neutropenic infection. In 21 (30.4%) and 19 (27.5%) episodes patients received either prophylactic or therapeutic granulocyte-colony stimulating factors (G-CSF), respectively.

Infections were microbiologically documented in 53 (76.8%) episodes. Out of the remaining 16 clinically documented infections, 13 were confirmed radiologically or with ultrasound (12 pneumonias and one cholecystitis), two patients had fever with clinical signs of septic shock and one had cellulitis. Details about the sites of infection are listed in Table 1.

Bloodstream and lower respiratory tract were the most common sites of infection. The most common microbiological isolates from blood cultures were gram-negative bacteria in 72% (*E.coli* in eight, *Pseudomonas aeruginosa* in three, *Stenotrophomonas maltophilia* in three, *Klebsiella pneumoniae* in two, *Acinetobacter baumannii* in one and unidentified non-fermenting gram-negative bacteria in one episode). Gram-positive bacteria were isolated from three out of 25 positive blood cultures (*Enterococcus faecalis*, *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus*). In one case anaerobic bacteremia was identified (*Clostridium tertium*). There were two cases of polymicrobial blood infection (with *E.coli*, *Enterococcus faecalis* and *Candida albicans* in one, and *Enterobacter asburiae*, *Proteus mirabilis* and *Enterococcus faecalis* in the other). Candidemia with *Candida albicans* was seen in one case.

Median time from the diagnosis of neutropenic infection to the ICU admission was 10 hours (range 0 hours – 27 days). Reasons for ICU admission were septic shock in 39 (56.5%) patients, severe sepsis in 20 (29%) patients, pulmonary thromboembolism in three patients and seven patients were already in the ICU at the onset of neutropenic infection. In 61 (88.4%), 30 (43.5%), 6 (8.7%) and 11 (15.9%) episodes vasopressors and/or inotropes, mechanical ventilation, dialysis and surgery were required, respectively.

Afebrile neutropenic infections

Sixty (87%) episodes of neutropenic infections were febrile and only 9 (13%) episodes, which oc-

curred in 9 patients, were afebrile. Median age of patients with afebrile infection was 56 years (range 41–82 years). All were considered high-risk with a median MASCC score of 13 (range 7–18). There were no differences between patients with afebrile and febrile neutropenic infection with regard to age, sex, comorbidities, status at the time of diagnosis of neutropenic infection, MASCC score, severity of neutropenia, type of infection, rate of Gram negative or polymicrobial bacteremias and time to the ICU admission. However, patients with afebrile neutropenic infection were more likely to have solid tumors (Table 2).

Five patients were afebrile throughout the episode of infection, in two patients there was a history of fever at home, and two patients developed fever on the 5th and 7th day of hospitalization, respectively, due to a secondary, health care-associated infection. The highest recorded temperature within 72 hours of diagnosis of neutropenic infection was 37.2°C or lower in five patients, and between 37.4 and 37.8°C in the remaining four patients.

Six patients (66.7%) received drugs with potential antipyretic effect (non-steroidal anti-inflammatory drugs, paracetamol, corticosteroids, metamizole) at least once within 48 hours prior and 72 hours after the diagnosis of neutropenic infection, five intermittently and only one continuously. Similarly, 56.7% of patients with febrile neutropenic infection received drugs with potential antipyretic effect ($p = 0.73$). There was no difference in the rate of afebrile neutropenic infections in patients who received drugs with antipyretic effect compared to patients who did not (15% vs. 10.3%, respectively, $p = 0.72$).

Presenting clinical signs and symptoms of infection in afebrile neutropenic patients were hypotension, severe fatigue with inappetence, shaking chills, altered mental state and cough, in descending order of frequency. All of them eventually deteriorated to severe sepsis or septic shock.

Eight patients (89%) had microbiologically documented infections: four had gram-negative bacteremias (two *E.coli*, one *Klebsiella pneumoniae*, one *Pseudomonas aeruginosa*), two had polymicrobial peritonitis, one had a gram-positive pneumonia and one had a gram-negative urinary tract infection but without blood culture drawn. One patient had a radiologically documented pneumonia.

Outcome

In all patients with severe neutropenic infection 30-day in-hospital mortality rate was 55.1%. In four

TABLE 2. Comparison between patients with afebrile and febrile neutropenic infection

Characteristics	Afebrile (n = 9)	Febrile (n = 60)	p-value	
Age (years)	> 65	4	24	1.0
	≤ 65	5	36	
Sex	Male	4	38	0.28
	Female	5	22	
Cancer type	Lymphoma	3	49	0.005
	Solid tumors	6	11	
CCI	Low (0)	5	23	0.47
	Medium - very high (≥ 1)	4	37	
ACE-27	None - mild (G0–1)	5	28	0.73
	Moderate - severe (G2–3)	4	32	
Status at diagnosis	Inpatient	3	34	0.29
	Outpatient	6	26	
MASCC score	< 15	5	30	1.0
	≥ 15	4	30	
Severe neutropenia	Yes	3	27	0.72
	No	6	33	
Type of infection	MDI	8	45	0.33
	CDI	1	15	
Bloodstream infection ^a	Gram negative ^b	4	16	0.55
	non-Gram negative	0	5	
Mean time to the ICU (hours)		41	54	0.73

ACE-27 = adult comorbidity evaluation-27 index; CCI = Charlson comorbidity index; CDI = clinically documented infection; ICU = Intensive Care Unit; MASCC = Multinational Association for Supportive Care in Cancer; MDI = microbiologically documented infection

^an = 25

^balso includes polymicrobial bacteremias with at least one Gram negative bacteria

patients, who experienced two separate episodes of severe neutropenic infection, two survived both episodes and two had fatal outcome during the second episode. Thirty (79%) deaths occurred in the ICU and the remaining deaths occurred after the ICU discharge. Cause of death was attributed to the uncontrolled infection in 31 patients, pulmonary thromboembolism in three, comorbidities in two, and cancer progression in two patients. In patients with afebrile neutropenic infection episode 30-day in-hospital mortality rate was 78%. While in six patients death occurred due to the uncontrolled infection, one patient died due to the cancer progression. The remaining two patients who survived had radiologically documented pneumonia and *Pseudomonas aeruginosa* bacteremia.

Prognostic factors associated with 30-day in-hospital mortality are listed in Table 3. Patients with afebrile neutropenic infection had a trend for a higher 30-day in-hospital mortality rate as compared to patients with febrile neutropenic infection (78% vs. 52%, $p = 0.17$). MASCC score < 15 (71% vs. 38%, $p = 0.006$), lactic acidosis (100% vs. 53%, $p = 0.04$) and use of mechanical ventilation (87% vs. 31%, $p < 0.001$) were all associated with significantly higher 30-day in-hospital mortality rates. We did

TABLE 3. Prognostic factors associated with 30-day in-hospital mortality

Prognostic factors		Died (n = 38)	Survived (n = 31)	p-value
Age (years)	> 65	17	11	0.44
	≤ 65	21	20	
Cancer type	Lymphoma	29	23	0.84
	Solid tumors	9	8	
CCI	Low (0)	17	11	0.44
	Medium - very high (≥1)	21	20	
ACE-27	None - mild (G0-1)	20	13	0.38
	Moderate - severe (G2-3)	18	18	
G-CSF prophylactic	Yes	14	7	0.2
	No	24	24	
G-CSF therapeutic	Yes	12	7	0.41
	No	26	24	
Fever status	Febrile	31	29	0.17
	Afebrile	7	2	
MASCC score	< 15	25	10	0.006
	≥ 15	13	21	
Bloodstream infection	Yes	15	10	0.54
	No	23	21	
Mechanical ventilation	Yes	26	4	P < 0.001
	No	12	27	
Lactic acidosis ^a	Yes	7	0	0.04
	No	31	27	
Time period of ICU admission (year)	2000–2003	4	4	1.0
	2004–2011	34	27	

ACE-27 = adult comorbidity evaluation-27 index; CCI = Charlson comorbidity index; G-CSF = granulocyte-colony stimulating factors; ICU = Intensive Care Unit; MASCC = Multinational Association for Supportive Care in Cancer;

^an = 65

not find any significant association between the mortality and age, cancer type, comorbidities as assessed by the two different comorbidity indexes, presence of bloodstream infection, use of G-CSF and time period of ICU admission.

Discussion

Fever in neutropenic cancer patients with infections is only rarely absent and may predict worse outcome.¹³⁻¹⁵ In our study we identified 69 episodes of severe neutropenic infection in 65 cancer patients, among which 9 (13%) episodes were afebrile. All afebrile neutropenic infection episodes were either microbiologically and/or radiologically documented and all progressed to severe sepsis or septic shock. Patients with afebrile neutropenic infection had a trend for a higher 30-day in-hospital mortality rate as compared to patients with febrile neutropenic infection (Table 3).

Majority of published studies to date, which evaluated cancer patients with neutropenic infections, included only patients with febrile neutrope-

nia. Sickles *et al.* studied clinical signs of the five most common localized infections (pharyngitis, skin infection, pneumonia, anorectal infection and urinary tract infection) in neutropenic and non-neutropenic cancer patients. They reported that fever was much more common in neutropenic patients than in non-neutropenic ones. When analyzing all infection sites together, fever (defined as > 38°C) was absent in 2–10% of all patients, depending on severity of neutropenia (in those with absolute neutrophil count ≤ 0.1 × 10⁹/l fever was absent in only 2%).⁵

Published data show that 18–40% and 10–20% of non-neutropenic patients develop normothermia or hypothermia, respectively, despite infection with severe sepsis or septic shock.^{9,16,24-29} However, definitions of fever, normothermia and hypothermia differed in published studies. Recently published study by Weinkove *et al.* reported 23% incidence of afebrile neutropenic sepsis in subgroup of patients with hematological malignancies (20% of these had a peak body temperature below 36.5°C and the remaining between 36.5 and 37.4°C during first 24 hours in the ICU).³⁰

According to our results, overall mortality rate in the ICU was 55.1% and was in line with published results of other studies.³¹⁻³⁵ Lower MASCC score (MASCC score <15), need for mechanical ventilation and lactic acidosis at the time of the ICU admission were associated with significantly higher 30-day in-hospital mortality (Table 3). These observations are in line with previously reported studies in patients with severe infections.^{32,34,36-39} Although studies have reported improved survival rates of critically ill cancer patients during the past decade as compared to later time periods, in part due to implementation of the Surviving Sepsis Campaign guidelines, we did not find any significant difference in mortality rates between patients treated in the ICU before and after 2004 (50 vs. 55%, respectively, p = 1.0) (Table 3).^{40,41} Furthermore, we observed a trend for a higher mortality rate in patients with afebrile neutropenic infections as compared to patients with febrile neutropenic infections (78 vs. 52%, p = 0.17) (Table 3). Published data show that patients with severe infections and hypothermia more likely develop septic shock as compared to those who are not hypothermic.^{25,27,29} Furthermore, reported mortality rates in this subpopulation are consistently higher compared to normothermic or febrile patients, and are in range between 50–80%.^{24-29,42} In contrast, data on patients with normothermic response to severe infection are inconsistent.²⁴⁻²⁸ Results of recently published large

multicentric retrospective registry study, which included 4027 patients with neutropenic sepsis, showed that patients with neutropenic sepsis and peak temperature below 36.5°C (hypothermia) within the first 24 hours of admission to the ICU had approximately two-fold higher risk for in-hospital death as compared to normothermic (defined as temperatures between 36.5 and 37.4°C) patients. They did not observe any significant difference in mortality between normothermic and febrile (peak temperature of $\geq 37.5^\circ\text{C}$) patients. Similar was observed in a subgroup of patients with neutropenic sepsis and hematological malignancy.³⁰ Due to the retrospective nature of our study and due to the small number of patients with afebrile infections further subset-analyses (hypothermic *vs.* normothermic *vs.* febrile) were not feasible.

Use of drugs with antipyretic effect (e.g. some drugs used for the management of pain, corticosteroids) could potentially block the development of fever, which may delay presentation of these patients with serious infections to medical services. However, in our study there were no differences in the use of drugs with antipyretic effect in the febrile and afebrile subgroups of patients. Also, we did not find any differences in the rate of afebrile neutropenic infections in patients who received drugs with antipyretic effect and those who did not. Results of recently published study showed that feeling unwell in the absence of fever, which is a key marker of neutropenic sepsis, might discourage patients from contacting a doctor.⁴³ Delay of treatment with effective antimicrobial therapy in patients with severe neutropenia and bacteremia or septic shock is associated with increased mortality rates.^{44,45} Patients on chemotherapy treatment should be informed that, although rarely, fever may be absent even in severe neutropenic infections and warned of possible other signs and symptoms of infection. In our study we observed that patients with afebrile neutropenic infection can present with hypotension, severe fatigue with inappetence, shaking chills, altered mental state or cough.

Our study has several limitations. First, this was a retrospective, single center study with a small sample size of heterogeneous patient population and therefore our findings are only hypothesis-generating. Only patients with solid tumors and lymphomas are treated at our center; patients with acute leukemias who frequently experience neutropenic infections were thus excluded from our analysis. Second, due to the small number of patients with afebrile infection a multivariate analysis

as well as further subset comparisons (e.g. hypothermic *vs.* normothermic *vs.* febrile patients) were not feasible. Third, due to retrospective nature of our study we were not able to assess the potential impact of delayed effective antimicrobial therapy on the outcome of febrile and afebrile patients. Fourth, definition of febrile and afebrile episodes in our study may be flawed as axillary body measurement, used in our study, correlates least accurately with core body temperature with as much as 0.9°C variation.⁴⁶ According to the international guidelines for the management of infections in neutropenic cancer patients body temperature should be measured orally, while axillary measurements are discouraged.^{13,15} Finally, we evaluated all episodes of severe neutropenic infections (with four patients having two separate episodes of febrile neutropenic infections), as occurring in real life practice, and thus risked potential statistical bias.²³

In conclusion, afebrile infections in neutropenic cancer patients are rare. However, in cancer patients with chemotherapy-induced neutropenia and severe infections, afebrile patients might be at higher risk of death due to the complications of infection as compared to patients with febrile neutropenia. In addition, we identified lower MASCC score (MASCC score < 15), need for mechanical ventilation and lactic acidosis at the time of the ICU admission as negative prognostic factors for outcome. Patients on potentially myelosuppressive systemic cancer treatment should be informed that occasionally fever may be absent during the episode of neutropenic infection, and that they should immediately seek medical attention if signs or symptoms suggestive of infection occur, even in the absence of fever.

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